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Original article

The higher prevalence of multiple sclerosis among Iranian Georgians; new clues to the role of genetic factors

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ABSTRACT

Background. – Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) with varied prevalence rates among populations with different ethnic backgrounds. Therefore, studies done on minorities have shed more light on the risk factors.
Objective. – Comparing MS prevalence in Georgian-based population immigrated to Iran and other Iranians.
Methods. – All records of MS patients enrolled in the two biggest registry systems were investigated. All of the patients born in Fereydunshahr and Buin va Miandasht (2 biggest cities with Georgian immigrants) were interviewed and their baseline characteristics were obtained. Patients' ethnic background information were obtained from the Iran National organization for civil registration.
Results. – Forty-one patients from Fereydunshahr and Buin va Miandasht were identified. The population of the two cities combined and the estimated number of Georgian-based patients in both cities were reported 59817 and 12000, respectively. The estimated ethnicity-adjusted prevalence among the Georgian-based individuals was 2.3 times higher than the non-Georgian ones. Baseline characteristics were also compared.
Conclusion. – There was a higher prevalence of multiple sclerosis among the Georgian minority of Isfahan. Due to the ethnic background of the Georgian minority, genetic risk factors should be considered more as a risk factor.

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1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) in which the damage of myelin sheaths around the axons leads to disability symptoms [1]. Depending on the quantity of axonal loss in the inflammatory infiltrations, the resulting symptoms differ in severity [2]. MS prevalence rates also differ widely among countries but are traditionally thought to rise with increasing longitude [3]. The prevalence of MS in the Middle East countries has been shown to be increased over time [4]. Regarding the diverse methodologies used in epidemiological studies in this area, more studies need to provide more concise results about the role of genetic factors in MS [5].

Iran is a Middle East country with a medium to high prevalence of MS [4]. According to a review article performed in 2013, the disease has the highest prevalence in Isfahan and Tehran provinces [6]. Isfahan was reported as one of the regions with the highest MS prevalence in the Middle East and North Africa by Heydarpour et al. [7]. To specify genetic and environmental risk factors of MS in this region, studies of immigrants in Isfahan province with different genetic backgrounds can be useful. These investigations may help to identify the most influential predisposing factors of MS among different races [8].

Fereydunshahr and Buin va Miandasht are cities in Isfahan province with more than 12000 Georgian immigrants that account for nearly 20% of their total population (reported 59817 by the year 2016) [9]. Both of these cities belong to the Fereydan region of Isfahan province. Initially, Fereydani Georgians were forced to move to Isfahan by Shah Abbas I during the 17th century. They then moved to Najaf Abad and finally, settled in Fereydan region [10].

To this date, no studies have calculated MS prevalence among the Georgian immigrants of Fereydunshahr and Buin va Miandasht, Isfahan. To the authors' best knowledge, no prevalence of MS was reported in Georgia either [11]. In the current study, the prevalence of MS was calculated among Georgians of these cities and compared with MS prevalence among non-Georgian Fereydani population (the population residing in Fereydan region without a Georgian ethnic background).

2. Methods

The proposal of the current study was ethically approved and supported by Isfahan MS Center (IMSC). Consent of all patients was obtained during the interviews for data collection regarding Helsinki's declaration.

This epidemiological cross-sectional study was conducted in Fereydan region (Fereydunshahr and Buin va Miandasht cities), Isfahan province, Iran. The cities have a relatively large Georgian population (nearly 20% of their population) of 12000 based on the data present at the governorate of Fereydunshahr and Buin va Miandasht up to the year 2016. Patients were enrolled for the study from the two main registries in Isfahan province; Isfahan University of Medical Sciences (IUMS) and IMSC. All patients were enrolled until the year 2017. We identified 41 patients who had been diagnosed with MS by a neurologist (according to McDonald's criteria). Patients' contact numbers were then obtained. We interviewed all 41 Georgian and non-Georgian patients (without any Georgian ancestry) and collected their baseline information (sex, age, age at MS onset, etc.). Patients' ethnic background information were obtained from the Iran National Organization for Civil Registration.

We used the 2016 available data at Fereydunshahr and Buin va Miandasht governorate and the 2016 census data which were the latest updated data on the population of Fereydani Georgians and the population of the two cities, respectively. The data were analyzed with Stata version 10 and SPSS version 20. Confidence intervals (CI) and p values were calculated using these programs (the statistical tests used for each variable are indicated in Table 2). All qualitative and quantitative variables were described along with their count, percentage and SD/range. A *P*-value of less than 0.05 was considered statistically significant in all data analysis.

3. Results

In this study, we investigated the place of birth of 7120 MS patients registered in IMSC and IUMS (5490 were female and 1630 were male); of them, 31 were originally from Fereydunshahr and 10 from Buin va Miandasht. After interviewing all 41 patients, 13 patients in Fereydunshar and 2 in Buin va Miandasht were Georgian-based. We reported the prevalence ratio based on the population of the cities (31 patients among 35654 people in Fereydunshahr and 10 patients among 24163 people in Buin va Miandasht) as 86.9/100000 (95% confidence interval (CI): 59.08–123.41) for Fereydunshahr and 41.3/100000 (95% CI: 19.85–76.11) for Buin va Miandasht. The ethnicity-adjusted prevalence rates for the Georgian-based population in the two cities (13 patients among 8500 people in Fereydunshahr and 2 patients among 3500 people in Buin va Miandasht) were 152.9/100000 (95% CI: 81.4–261.5) for Fereydunshahr and 57.14/100000 (95% CI: 6.92–206.42) for Buin va Miandasht.

Table 1 indicates the baseline features of all 15 Georgian-based patients.

4. Differences between Georgian and non-Georgian patients

Table 2 shows the comparisons between demographic and clinical characteristics of Georgian and non-Georgian patients.

The prevalence rate of MS among Georgian-based patients was calculated 2.3 times higher than non-Georgian patients.

The most frequent first clinical presentation was ''optic neuritis'' among non-Georgian patients and ''double vision'' among Georgian patients three of whom had lesions on their brainstem in their first MRIs. The mean expanded disability status scale (EDSS) was reported as 2 in Georgian and 1.5 in non-Georgian patients. The most frequent MS course in both groups of patients was Relapsing Remitting. The mean age in Georgian patients was calculated to be 36.8 years, and for non-

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Table 1 – Demographic and clinical characteristics of the Georgian-based MS patients.

Sex	Age	Age at MS onset	Ethnicity	Place of birth	1st clinical presentation	EDSS	Family history	Duration of follow-up	MS course	Primary medication	Current medication
F	32	30	G	Fe	Double vision	3	Neg	4	RRMS	Betaferon	Betaferon
F	33	33	G	Fe	Paranesthesia of right upper limb	1	Neg	13	RRMS	NA	Avonex
M	34	30	G	Fe	Weakness of right upper limb	2	Neg	8	RRMS	Betaferon	Betaferon
F	23	23	G	Fe	Double vision	1	Neg	8	RRMS	Avonex	Avonex
F	40	40	G	Fe	Optic neuritis	1	Neg	8	RRMS	Azathioprine	Azathioprine
F	37	24	G	Fe	Optic neuritis	1	Neg	4	RRMS	Avonex	Avonex
F	54	35	G	Fe	Weakness of lower limbs + ataxia	5	Neg	12	PPMS	NA	No medication
F	35	26	G	Fe	Optic neuritis + paresthesia of limbs	1	Neg	12	RRMS	Avonex	Avonex
F	43	31	G	Fe	Double vision	4	Neg	12	SPMS	NA	Baclofen
M	44	42	G	Fe	Double vision + paresthesia of limbs	2.5	Neg	12	RRMS	Rebif	Rebif
F	37	25	G	Fe	Weakness of lower limbs	2.5	Post	12	RRMS	Avonex	Fingolimod
F	37	33	G	Fe	Double vision	0	Neg	12	RRMS	Rebif	Rebif
F	35	31	G	Fe	Double vision	2	Neg	12	RRMS	Avonex	Avonex
F	25	23	G	Bm	Double vision	2	Neg	9	RRMs	Avonex	Fingolimod
F	44	29	G	Bm	paresthesia + weakness of right upper limb	2.5	Neg	12	RRMS	Avonex	Fingolimod

Abbreviations: F: female; M: male; G: Georgian; N-G: non-Georgian; Fe: Fereydunshahr; Bm: Buin va Miandasht; Neg: negative; Post: positive; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; NA: not available. Descriptions: Betaferon: interferon beta 1-b; Avonex: interferon beta 1-a weekly; Rebif: interferon beta 1-a every other day.

Georgian patients, it was 38.0 years; there was no significant difference in age between the two groups of patients. Also, the most frequently consumed primary medication among Georgians and non-Georgians was Avonex (interferon beta 1-a weekly) as used by 19 patients. Four of these 19 patients (22%) later changed their medications to Fingolimod, one of whom had developed secondary progressive MS.

5. Discussion

Our study is among the few epidemiologic works done on immigrants with different nationalities in Iran. To this date, no other study has reported an estimated prevalence of MS among the Georgian-based population in Iran. We found a higher MS prevalence the Georgian race in comparison to the non-Georgians residing in both cities of Fereydunshahr and Buin va Miandasht. Analysis of the baseline characteristics of the patients showed no significant difference between the groups except for ''first clinical presentation.''.

Epidemiologic studies have revealed different aspects of MS etiology over time associated with race, age, sex, geography and other risk factors [12]. Studies on immigrants in different regions have helped narrow the effective risk factors for MS prevalence. According to these studies, migration from a high-risk to a low-risk area reduces the risk of MS incidence, and conversely, migrating to a high-risk region will increase MS prevalence. This suggests that both the genetic background and the environmental risk factors (of the place of birth and the place of current residency) affect disease prevalence [13,14].

The ancestors of Iranians with a Georgian ethnic background were forced to migrate to Iran in the 17th century. They were settled in Asad-abad, Gilan, Mazandaran, Khorasan, Fars and Fereydan in Isfahan province, from which most Georgians lost their traditions except for a considerable group in Fereydan region of Isfahan who kept their Georgian identity and has still been called Fereydani Georgians [10,15]. It has been reported that for many years Georgians mostly married each other that Georgian-Persian marriages happened at a very low frequency [15]. Moreover, during interviewing the locals, we realized that until the previous generation the Fereydani Georgians were almost entirely isolated and only married to residents with Georgian ancestries. Hence, the locals and the Fereydani Georgians have different genetic backgrounds. The results indicated that MS prevalence reported was nearly 2.3 folds higher among the Georgian population.

Fereydani Georgians went under Islamization early on after their forced migration [10]. Therefore, their culture and life traditions changed rapidly and are nowadays almost similar to that of the non-Georgians of the region. Considering this, the differed genetic background may have played a more direct role. To our best knowledge, there have been no reports of MS prevalence in Georgia so far. It is highly recommended to compare the prevalence of MS in Georgia country with our findings to provide more knowledge about the effect of environmental factors over time.

The prevalence ratio of the Armenian minority in Isfahan province was likewise reported to be several folds higher than the ratio reported for the local Isfahanies. Similarly, the

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Table 2 – Demographic and clinical characteristics compared between Georgian and non-Georgian patients.

Characteristics	MS patients		P-value
	Georgian (n = 15)	Non-Georgian (n = 26)	
Baseline population	12000	47817	
Fereydunshahr (35654)	8500	27154	
Buin & Miandasht (24163)	3500	20663	
Age (year)	36.8 ± 7.6	38.0 ± 5.7	0.45*
Gender; F/M	13/2	21/5	0.62†
Prevalence (per 100,000)	125	54.37	> 0.01#
95% Confidence Interval	70–206.2	35.52–79.67	
Rate ratio (Georgian/non-Georgian)	2.30		
Mean EDSS	2 [1–1.6]	1.5 [1.1–2]	0.85††
Types of MS			0.10**
Relapsing-Remitting (RR)	13	19	
Secondary-Progressive (SP)	1	7	
Primary-Progressive (PP)	1	0	
Family history	1 (7.1)	6 (25.0)	0.22**
First Clinical Presentation			0.02†
Optic neuritis	3	13	
Double vision	7	1	
Paresthesia of the limbs	4	5	
Weakness of the limbs	4	4	
Ataxia	1	3	
Hemiplegia	0	1	
Impairment of gustation and Face paresthesia	0	1	

The data are presented as Mean ± SD, Number, Number (%) and Median [IQR]. M: Male; F: Female. *P*-values calculated by: *Independent sample t-test, † Chi-Square test, #Proportional test, †† Mann–Whitney U Test, and **Fisher exact test.

differences in genetic background and lifestyle were considered more likely to be responsible for the significant difference [16]. Cominifrota et al. performed a similar study on MS patients in four cities in Brazil and reported a higher prevalence of MS among the Italian-based population in comparison to other European ancestries and the local Brazilians [17]. Moreover, Iran has experienced a high rate of emigration in the past 40 years. Therefore, several studies have been conducted on Iranian immigrants in British Colombia (BC), Canada, Sweden, Norway and England [18]. Two studies have reported a higher prevalence of MS among the Iranian immigrants in their countries. In a study in 2010 in Gothenburg, the higher MS prevalence among Iranian immigrants was attributed to the lifestyle and environment differences between Iran and Sweden [19]. In another study in 2014 in BC, Canada, a higher prevalence of MS was stated among the Iranian immigrants (433/100000). Environmental and genetic risk factors were the reason given for the significant differences [20].

The author published another study, which conversely indicated the MS prevalence to be lower in the Afghan minority of Isfahan province. Two main reasons were given in order to explain the results. Regarding the hygiene theory, the Afghan minority have a lower chance of developing an autoimmune disease such as MS because of the lower coverage of vaccination in their country that has caused them to be more exposed to different viruses and bacteria. Non-identical genetic risk factors (HLA-DRB1 and HLA-DQB1) were also a theory to be considered [21]. A study in Norway on the Iranian minority also reported a lower prevalence among the immigrants compared to the local population, which can be due to genetic variations. However, a higher prevalence compared to the population in the country of birth, was reported. The increase in MS risk following migration has been convinced by environmental risk factors in Norway such as smoking, child obesity or low vitamin D levels [22].

For the first time, we estimated a prevalence rate of MS for the Georgian-based minority in Isfahan in our study. However, the result of this study is not absolutely conclusive because of the underestimation of the number of patients born in Fereydunshahr and Buin va Miandasht. Not all the MS patients in Isfahan province were registered in IMSC and IUMS (however, these were the two biggest patient registries in the province). Therefore, it is possible that some patients were missed and not included in our analyses. A more expanded search in patient registries other than IMSC and IUMS needs to be done in order to achieve a more accurate conclusion and prevalence rate. Also, some characteristic data were missed and not entered for analyses.

We conclude that genetic may play an important role in progression of MS among varied races of human being.

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Disclosure of Interest

The authors declare that they have no competing interest.

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